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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,007	11/04/2003	Charles Allerson	ISIS-5325	5641

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WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER

ZARA, JANE J

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/701,007

Applicant(s)

ALLERSON ET AL.

Examiner

Jane Zara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-7, 11-14, 28-34, 37, 38, 46, 49-51, 53-65, 67, 68, 72, 74-78, 92-96 and 100-103 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>9-14-04</u> . | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 2-7,11-14,28-34,37,38,46,49-51,53-65,67,68,72,74-78,92-96 and 100-103.

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DETAILED ACTION

This Office action is in response to the communication filed 8-3-06.

Claims 2-7, 11-14, 28-34, 37, 38, 46, 49-51, 53-65, 67, 68, 72, 74-78, 92-96, 100-103 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

Claims 2-7, 11-14, 28-34, 37, 38, 46, 49-51, 53-65, 67, 68, 72, 74-78, 92-96, 100-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al, Fosnaugh et al and Morrissey et al for the reasons of record set forth in the Office action mailed 5-5-06 and for the reasons set forth below.

The claims are drawn to compositions and methods of inhibiting gene expression in a tissue or an animal comprising administration of compositions comprising an siRNA oligonucleotide between 10-40 linked nucleosides comprising the generic motif, $F(SF)_n(S)_{nm}$, wherein F is a first type of nucleoside and S is a second type of nucleoside differing from the first in the 2'-substituent group, wherein n is from 2 to about 20 and

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nm is 0 or 1, and the motif comprises at least three nucleosides of said first type and at least three nucleosides of said second type, or which compositions comprise compounds comprising various motifs comprising nucleosides different in their 2'-substituent groups, and optionally include H, OH as first and second types of nucleosides, or alternatively comprising motifs of 2'-substituent groups which are optionally fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps, optionally including inverted deoxy abasic moieties.

Applicant's arguments filed 8-3-06 have been fully considered but they are not persuasive. Applicants argue that the instant invention is not found obvious in view of the prior art cited (in view of Elbashir et al, Fosnaugh et al and Morrissey et al) because the claims are not limited to methods, but also include compositions. Applicant also argues that the unique motifs now claimed have not been shown or suggested in the references of record, and that no suggestion or motivation, reasonable expectation of success of teaching or suggestion of all of the claim limitations have been provided by the references of Elbashir et al, Fosnaugh et al and Morrissey.

Contrary to Applicant's assertions, the motivation, suggestion of all of the claim limitations and a reasonable expectation of success have all been provided by the combined teachings of Elbashir et al, Fosnaugh et al and Morrissey et al.

Elbashir et al teach siRNA molecules comprising 2'-deoxy and 2'-O-methyl substitutions as well as teaching a correlation between the placement of 2'-substitutions on the oligonucleotides and retaining siRNA activity. Fosnaugh et al teach various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini, and the effect of arrangements of these different modifications on siRNA ability to bind to and inhibit target gene expression. Morrissey et al teach various ways of designing and optimizing 2'-O-modifications on siRNA, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini, and the effect of various motifs or arrangements of these 2'-substituents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA.

The combined teachings of these references provide the tools for optimizing and designing motifs, including the motifs claimed, as design choices on an siRNA molecule. These well known modifications are routinely incorporated into oligonucleotides and one of ordinary skill in the art would have been motivated to design various motifs or arrangements of these modifications to enhance stability of the siRNA molecules while maintaining inhibitory activity of the siRNA molecules. Furthermore, a reasonable expectation existed in the art at the time the instant invention was filed that

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various design choices or motifs, including the modifications and motifs claimed, would provide for functional siRNA with enhanced stability. One of ordinary skill in the art would have expected that the siRNA modified at appropriate configurations including the motif listed in claim 102 would provide target gene cleavage in the presence of an appropriate target gene sequence and in the presence of appropriately modified siRNA and RISC. And one of ordinary skill in the art would have produced various motifs as a matter of design choice and optimizing 2'-O modified motifs within the siRNA while maintaining its inhibitory activity would have been a matter of routine experimentation.

For these reasons, the instant 103 rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
10-13-06

J Zara
TC1600
JANE ZARA, PH.D.
PRIMARY EXAMINER